VOLUME 24 · NUMBER 35 · DECEMBER 10 2006

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Targeted Therapy for Metastatic Renal Cell Carcinoma

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Submitted August 8, 2006; accepted August 23, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/06/2435-5601/$20.00

DOI: 10.1200/JCO.2006.08.5415

A B S T R A C T

The discovery of a relationship for the *VHL* tumor suppressor gene, hypoxia inducible factor-1 alpha, and vascular endothelial growth factor in the growth of clear-cell renal cell carcinoma (RCC) has identified a pathway for novel targeted therapy. This study evaluated the impact of these agents on metastatic RCC (mRCC), and highlights recent phase II and III trials. A systematic review examined the clinical data for novel targeted agents in mRCC, with a focus on randomized phase II and III trials of the novel targeted agents sunitinib, temsirolimus, sorafenib, and bevacizumab. Several agents, including the small-molecule targeted inhibitors sunitinib, temsirolimus, sorafenib, and the monoclonal antibody bevacizumab, have demonstrated antitumor activity in randomized trials. Superior activity was found with sunitinib and temsirolimus versus cytokines in first-line therapy. Improved progression-free survival was reported with sorafenib and bevacizumab given second-line compared with placebo. Targeted therapies show promising activity in this disease, and they have been changing patient management. Sunitinib and sorafenib were recently approved by the US Food and Drug Administration for treatment of mRCC, These drugs are currently included in clinical practice.

J Clin Oncol 24:5601-5608. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Advances in understanding the biology and genetics of renal cell carcinoma (RCC) have led to novel targeted approaches for the treatment of metastatic RCC (mRCC). Recently, two targeted agents, sorafenib and sunitinib, were approved by the US Food and Drug Administration for treatment of advanced RCC. We reviewed the clinical data focusing on these agents and two others, bevacizumab and temsirolimus, which show activity in randomized trials.

HISTORICAL PERSPECTIVE

The predominant type is clear-cell carcinoma, comprising more than 85% of metastatic RCC. The remaining cases include papillary and chromophobe cell types. Cytotoxic chemotherapy agents and hormonal therapies have demonstrated a lack of effectiveness in treatment for mRCC.[1] Until recently, the only effective treatment was cytokine therapy with interferon-alfa (IFNα) or interleukin-2 (IL-2).

Cytokine Therapy

IL-2 and IFNα were first reported to have antitumor activity in the 1980s.[1] Both agents produced objective responses in 10% to 15% of patients.[1] The median survival with cytokine therapy is approximately 12 months.[1] Two randomized trials showed a modest survival benefit associated with IFNα.[2,3] High-dose IL-2 treatment was associated with a durable complete response proportion of 4%,[4] and was approved by the US Food and Drug Administration. High-dose IL-2 is associated with severe toxicity, and requires inpatient administration with intensive supportive care. The clinical benefit seems to be confined to a relatively small proportion of highly selected patients. Randomized phase III trials failed to show an improvement in median survival or progression-free survival for high-dose IL-2 compared with low-dose outpatient schedules or combination cytokine programs.[5,6] Attempts to identify a more effective cytokine program through combination programs have failed to show a survival benefit, and toxicity is more severe.[7] Until recently, no agent showed evidence of clinical benefit for patients with progressive mRCC after cytokine therapy, including a change in treatment to a different cytokine.[8]

Efficacy End Points

Response and survival data obtained from patients treated with cytokine therapy provided useful information for clinical trial design and interpretation of recent trials in targeted therapies. IFNα, the comparator arm for many trials in RCC, is associated with a median progression-free survival of nearly 5 months, and a median survival of 12 months.[9] Clinical trials of agents proven to lack activity in second-line therapy have shown that the median progression-free survival is 2 to 3 months, with a median survival of 12 to 13 months.[10-12]

Risk models were created for use in eligibility, stratification in randomization for phase III trials, and assessment of outcome. A model derived from data at Memorial Sloan-Kettering Cancer Center

(MSKCC; New York, NY) and validated by investigators at the Cleveland Clinic Foundation (Cleveland, OH) is used widely.[9,13] In this model, five variables are considered risk factors for short survival: low Karnofsky performance status, high lactate dehydrogenase, low serum hemoglobin, high "corrected" serum calcium, and time from initial RCC diagnosis to start of therapy of less than 1 year (or prior nephrectomy).[9] Patients are grouped according to pretreatment clinical features into three groups: favorable (no risk factors, median survival 30 months); intermediate (one or two risk factors, median survival 14 months), or poor (three or more risk factors, median survival 6 months).[9]

RCC BIOLOGY PROVIDES RATIONALE FOR TARGETED APPROACH

The cloning of the von Hippel-Lindau (*VHL*) tumor suppressor gene and the elucidation of its role in upregulating growth factors associated with angiogenesis are discoveries that provided insight into RCC biology and defined a series of potential targets for novel therapeutic approaches. Both sporadic and inherited forms of clear-cell RCC are associated with mutations in the *VHL* gene, located on chromosome 3p.[14] Individuals who inherit one defective copy of the *VHL* gene have a substantial risk for developing RCC and a variety of other neoplasias.[15] Direct sequencing experiments from sporadic tumor samples show that up to 75% of these patients have biallelic loss of function and mutation of *VHL* genes, and up to 20% exhibit expression inactivation by hypermethylation.[16,17]

The *VHL* gene product is found in a multiprotein complex that ubiquitinates transcriptional factor hypoxia-inducible factor 1 alpha (HIF-1α).[17] The normal function of HIF-1 complex (a heterodimer composed of alpha and beta subunits) is to regulate expression of several genes in response to hypoxic stress.[15] Under normal conditions (ie, with wild-type *VHL* and normal oxygen tension), HIF-1α is enzymatically hydroxylated. HIF-1α is subsequently ubiquitinated by the VHL protein complex and degraded within proteasomes. Under hypoxic conditions, HIF-1α is not hydroxylated, and cannot bind and be ubiquitinated by the VHL protein complex. Bi-allelic inactivation of *VHL* (as occurs in clear-cell RCC) likewise prevents degradation of HIF-1α.

In addition to regulation by the VHL complex, HIF-1 activity is regulated by growth factor and cell adhesion pathways. On binding of a growth factor to a tyrosine kinase receptor, HIF-1α protein levels increase through the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway and the Ras/Raf/mitogen-activated protein kinase pathways.

Once stabilized, HIF-1α translocates into the nucleus, where it combines with the constitutively present HIF-1 beta (HIF-1β) to form the active transcriptional factor HIF-1 heterodimer. HIF-1 binds to a variety of additional transcriptional cofactors that activate transcription of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), platelet-derived growth factor (PDGF), glucose transporters (eg, GLUT-1), transforming growth factor alpha (ligand for EGFR), and erythropoietin.[18] Many of these proteins are involved in angiogenesis, survival, pH regulation, and glucose metabolism. The absence of functional VHL protein in the inherited and sporadic forms of clear-cell carcinoma simulates hypoxia with resultant constitutive upregulation of these genes (Fig 1).

CLINICAL EXPERIENCE

Many targeted agents have been studied, including monoclonal antibodies that bind to growth factors and small molecules that act on the kinase portion of receptor tyrosine kinases (a summary of selected agents appears in Table 1). Of these, several multitargeted small molecules that inhibit VEGF receptor (VEGFR) and PDGF receptor (PDGFR; ie, sunitinib, sorafenib) show promising antitumor activity in mRCC. Bevacizumab, a monoclonal antibody to VEGF, also shows antitumor activity. Trials with the mTOR inhibitor temsirolimus demonstrated activity against mRCC. The results of phase III randomized studies with sorafenib, sunitinib, and temsirolimus showed activity compared with standard therapy, and these agents are summarized herein (Table 2; Fig 1).[19-21] In addition, we highlight bevacizumab, on the basis of activity in randomized phase II trials.[12,22]

In contrast, multiple trials of single agents targeting EGFR, including gefitinib, cetuximab, and others, failed to show single-agent activity.[23-25] One randomized trial found no improvement in survival for lapatinib, an inhibitor of EGFR/Erb2 tyrosine kinases, over hormonal therapy (Table 2).[26] A subset analysis performed in this trial in patients with tumors showing overexpression of EGFR suggested benefit in this group,[26]and may be considered as hypothesis-generating. Limited experience of imatinib, which inhibits PDGFR without VEGFR inhibition, failed to show single-agent activity.[27]

Sorafenib

Sorafenib is a bisaryl urea first designed as an in vitro inhibitor of the RAF-1 protein. Sorafenib was subsequently found to inhibit VEGFR and PDGFR. The dose level recommended for phase II trials was 400 mg twice daily, and activity was observed against mRCC.[28] Sorafenib was studied in a large phase II trial.[29] The trial design was "randomized discontinuation," intended to evaluate the primary effect of tumor growth inhibition rather than tumor shrinkage.[29] All patients enrolled onto the study received sorafenib for 12 weeks. Disease evaluation was conducted, and patients who had at least 25% tumor shrinkage continued with open-label drug. Patients with less than a 25% decrease or less than a 25% increase in tumor size were randomly assigned to either continue sorafenib for 12 weeks or a treatment change to placebo. Patients who progressed with an increase of tumor size of 25% or more were considered as having progressive disease and were removed from study. More than 500 patients with various solid tumors, of which 202 had mRCC, were treated in this study.[29] Seventy-three patients had tumor shrinkage of more than 25% during the initial 12 weeks of therapy. Another 65 patients with stable disease during this run-in period were randomly assigned at week 12 to therapy with either placebo or continuation of sorafenib. The median progression-free survival from random assignment was significantly longer with sorafenib (24 weeks) compared with placebo (6 weeks).[29] Adverse effects included skin rash, hand-foot skin reaction, and fatigue.[29] The study demonstrated significant disease-stabilizing activity in mRCC and tolerability with chronic daily therapy.

On the basis of the results of this study, a randomized phase III trial comparing sorafenib with placebo was initiated. Approximately

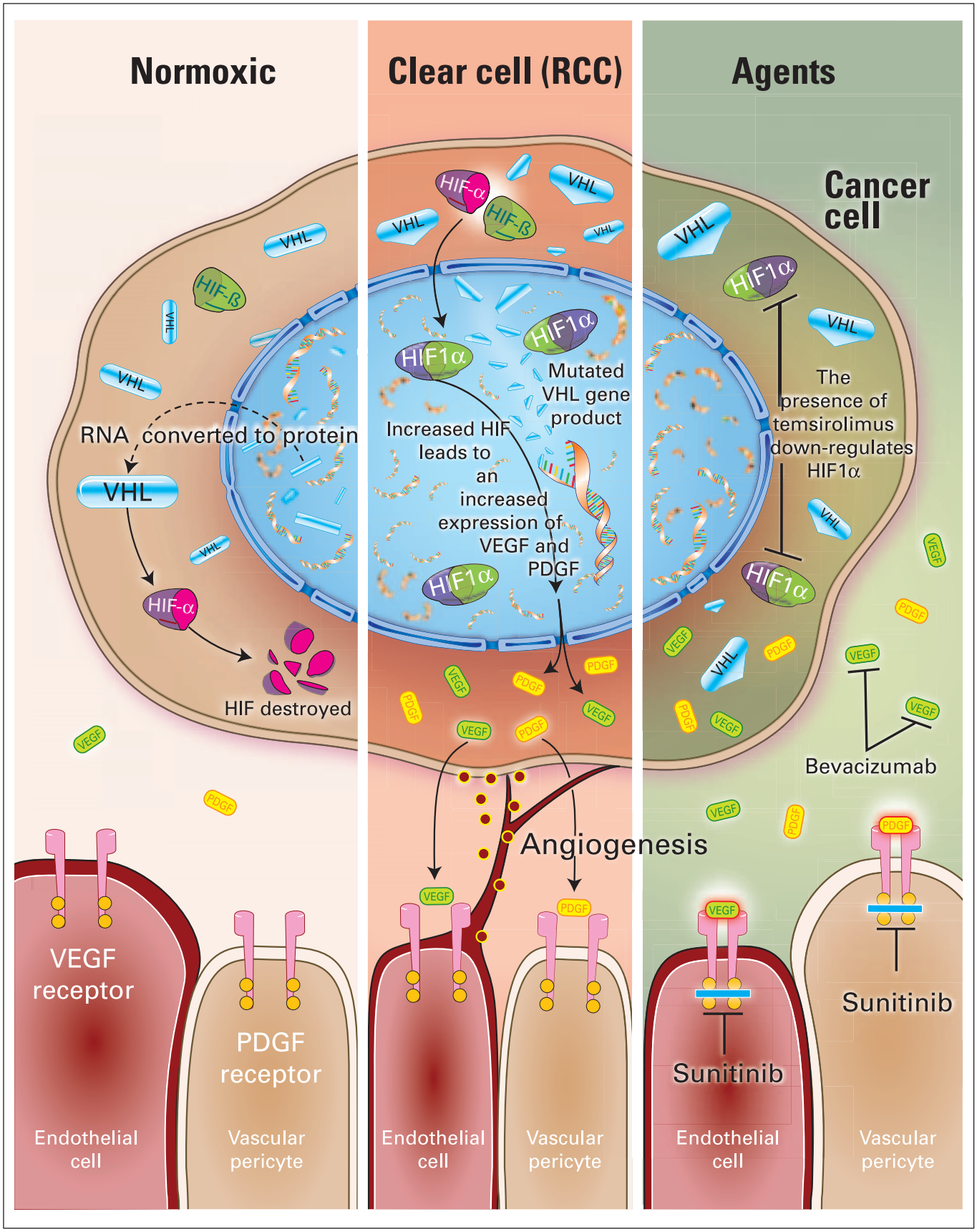

Fig 1. VHL pathway in clear-cell cancer of the kidney with examples of agents, temsirolimus (or RAD001), bevacizumab, sunitinib (or sorafenib, pazopanib), and where they target the pathway are demonstrated.

Table 1. Selected Targeted Agents and Phase of Study for Metastatic Renal Cell Carcinoma

Agent	Class	Proposed Mechanism of Action	Clinical Trial (phase)
Sunitinib	Small molecule	Tyrosine kinase inhibitor of VEGFR, PDGFR	II, III
Sorafenib	Small molecule	Tyrosine kinase inhibitor of VEGFR, PDGFR, Ras	II, III
AG-0736	Small molecule	Tyrosine kinase inhibitor of VEGFR, PDGR	II
Pazopanib	Small molecule	Tyrosine kinase inhibitor of VEGFR, PDGFR	II, III
PTK787	Small molecule	Tyrosine kinase inhibitor of VEGFR, PDGFR	I
Imatinib	Small molecule	Tyrosine kinase inhibitor of PDGR,	II
Gefitinib	Small molecule	Tyrosine kinase inhibitor of EGFR	II
Erlotinib	Small molecule	Tyrosine kinase inhibitor of EGFR	II
Cetuximab	Monoclonal antibody	Antibody to EGFR	II
ABX-EGF	Monoclonal antibody	Antibody to EGFR	II
Bevacizumab	Monoclonal antibody	Antibody to VEGF	II, III
VEGF-trap	Monoclonal antibody	Antibody to VEGF	I, II
G250	Monoclonal antibody	Antibody to CA IX	II
Bortezomib	Small molecule	Inhibitor to 26s proteasome component	II
Temsirolimus (CCI-779)	Small molecule	mTOR inhibitor	II, III
RAD001	Small molecule	mTOR inhibitor	II
Lapatinib	Small molecule	Tyrosine kinase inhibitor of EGFR/Erb/2	II, III

Abbreviations: VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; CA IX, carbonic anhydrase IX; mTOR, mammalian target of rapamycin.

900 patients with treatment-refractory metastatic clear-cell RCC were accrued (n = 451 sorafenib arm, n = 452 placebo arm).[11] A planned interim analysis after 353 events was conducted. The interim analysis demonstrated that the median duration of progression-free survival was 24 weeks in sorafenib patients compared with 12 weeks in the placebo group ($P < .000001$; hazard ratio 0.44). Independent review of the response data demonstrated that 80% of patients were progression free in the sorafenib arm (2% partial response and 78% stable disease) compared with 55% in the placebo arm (0% partial response and 55% stable disease).[11] The most common adverse effects included hand-foot skin reaction (26%), diarrhea (30%), alopecia (23%), fatigue (18%), nausea (14%), and hypertension (8%).[11]

An update of the impact of sorafenib on overall survival was reported.[30] As of the data cutoff, there were 367 deaths.[30] The median overall survival was 19.3 months for sorafenib and 15.9 months for placebo.[30] Although these data did not attain a level of significance at this interim analysis, a favorable trend in survival benefit has been observed.[30] After the interim analysis,[30] patients treated with placebo crossed over to sorafenib. This likely has an effect on the survival analysis. These data demonstrated the efficacy of sorafenib in mRCC, and led to regulatory approval of sorafenib by the US Food and Drug Administration.

Additional investigations are underway to better define the efficacy of sorafenib in first-line therapy, as adjuvant therapy following a nephrectomy and in combination with other targeted agents or cytokines. A randomized phase II trial of sorafenib versus IFNα conducted in 188 patients showed a favorable safety profile, and the efficacy data will be forthcoming.[19]

Sunitinib

Sunitinib (SU11248) is an oral multitargeted inhibitor of VEGFR and PDGFR. The 50-mg daily dose administered 4 weeks on/2 weeks off schedule was selected for phase II trials in mRCC.[31,32] Two consecutive open-label, phase II studies were conducted with sunitinib in patients with mRCC and progressive disease while patients were receiving cytokine-based immunotherapy.[31,32] In the first trial of 63 patients, 25 (40%) achieved partial responses with sunitinib, and an additional 17 (27%) had stable disease lasting at least 3 months. Median time to tumor progression was 8.7 months (95% CI, 5.5 to 10.7), and median overall survival was 16.4 months.[31]

A second, larger single-arm trial was conducted in clear-cell mRCC to confirm the antitumor activity and safety observed in the first phase II trial.[32] The eligibility and treatment plan was nearly identical to that of the first trial. Of 105 assessable patients receiving a median 7 months of therapy, the investigator-assessed response rate

Table 2. Randomized Phase III Trials of Targeted Agents in Patients With Metastatic Renal Cell Carcinoma

Trial	Setting	No. of Patients	End Point	Benefit in Targeted Therapy
Sorafenib *v* placebo[11]	2nd-line, after cytokines	903	Progression-free survival	Yes
Sunitinib *v* interferon[51]	1st-line, all MSKCC risk groups	750	Progression-free survival	Yes
Temsirolimus *v* interferon[21]	1st-line, modified MSKCC poor-risk group only	626	Survival	Yes
Lapatinib *v* hormone[26]	2nd-line, after cytokines	417	Time to progression	No

Abbreviation: MSKCC, Memorial Sloan-Kettering Cancer Center, New York, NY.

was 44%. A further 23 patients (22%) had stable disease for at least 3 months. The median duration of response for the 46 responders was 10 months, and median investigator-assessed progression-free survival was 8.1 months (95% CI, 5.5 to 10.4).[32] An independent third-party assessment resulted in 36 patients with partial response (34%; 95% CI, 25 to 44), and a median progression-free survival of 8.3 months (95% CI, 7.8 to 14.5 months).[32]

The most commonly reported treatment-related grade 3 adverse events were fatigue, nausea, diarrhea, and vomiting. The most frequently reported grade 3/4 laboratory abnormalities included lymphopenia, elevated lipase, neutropenia, and anemia.[31,32]

A randomized phase III trial was conducted to compare the results of sunitinib with IFNα in first-line treatment of clear-cell mRCC.[20] Seven hundred fifty patients were registered, 375 randomly assigned to sunitinib and 375 patients to IFNα.[20] The primary end point was progression-free survival as assessed by a third-party independent review. In a planned preliminary analysis, median progression-free survival, as assessed by third-party independent review, was 11 months for sunitinib versus 5 months for IFNα (hazard ratio 0.415; $P < .0001$).[20] The response rate by third-party independent review was 31% for sunitinib versus 6% for IFNα ($P < .0001$). The response rate by investigator assessment was 37% for sunitinib versus 9% for IFNα ($P < .000001$).[20] The results demonstrate a significant improvement in progression-free survival and objective response rate for sunitinib over IFN in first-line treatment of mRCC. The toxicity profile was similar to that reported in second-line studies. Based on the results of this interim analysis, sunitinib is standard therapy for first-line treatment for mRCC.

An alternate dosing schedule of sunitinib is being studied. In a study of 88 patients treated with a continuous daily sunitinib 37.5-mg dose, preliminary efficacy data showed some degree of tumor shrinkage in the majority of patients.[33] Sunitinib administered at this continuous dose of 37.5 mg was relatively well tolerated, with only a few patients requiring treatment breaks or dose reduction.[33] However, further investigation is required before the continuous dosing regimen can be recommended for general use.

Temsirolimus

mTOR, a large polypeptide kinase, is a therapeutic target for RCC. mTOR is a downstream component in the PI3K/Akt pathway, which acts by regulating translation, protein degradation, and protein signaling. VEGF-mediated endothelial cell proliferation requires the activity of PI3K, suggesting a direct antiangiogenic pathway.[34] mTOR has also been identified as an upstream activator of HIF, preventing degradation, and increasing HIF activity.[35] Preclinical data with a derivative of rapamycin (temsirolimus) has shown antitumor effects in renal and other cancer models.[36]

In a randomized phase II trial, 111 patients with advanced, heavily pretreated, refractory RCC were treated with 3 different dose levels (25.0, 75.0, 250 mg) of temsirolimus (CCI-779).[37] Seven percent of patients achieved a partial or complete response. No significant differences in outcome were noted between dose levels were noted. The median time to progression was 5.8 months, with a median survival for the entire population of 15.0 months.[37] Temsirolimus was combined with IFNα in a phase I/II clinical trial of 71 mRCC patients. Partial responses were observed in 11% of all patients, with a median time to progression of 9.1 month.[38] The median progression-free survival in this trial, which included patients previously treated with IFNα, was encouraging, and led to the inclusion of this treatment program as an arm in the randomized phase III trial.

This phase III randomized trial compared temsirolimus as a single agent (25.0 mg) versus temsirolimus (15.0 mg) plus IFNα versus IFNα as first-line treatment in patients with poor-risk features.[21] Poor-risk eligibility for the trial was based on modified MSKCC criteria.[9] Six hundred twenty-six patients were randomly assigned. The median survival for temsirolimus was 10.9 months compared with 7.3 months with IFN and 8.4 months with temsirolimus plus IFN.[21] There was a significant improvement in survival for temsirolimus compared with IFN, with a P value of .0069 and a hazard ratio of 0.73 in favor of temsirolimus.[21] The study showed that temsirolimus significantly increases the survival of first-line, poor-risk advanced RCC patients compared with IFNα.[21] Further studies are needed to define the role of temsirolimus in first-line therapy for patients with a more favorable prognosis (intermediate and poor risk), combined with other targeted agents and as sequential therapy after treatment with sunitinib or sorafenib.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody agent that binds and neutralizes all the major isoforms of VEGF-A. The clinical use of bevacizumab in patients with clear-cell carcinoma of the kidney was investigated in a randomized, double-blind, phase II trial that compared a placebo with bevacizumab.[12] Two dose levels of the antibody were studied (3 and 10 mg/kg), and therapy was administered every 2 weeks. Eligible patients included those who had a histologic confirmation of clear-cell carcinoma and either had received previous therapy with IL-2 or for whom the use of IL-2 was contraindicated. The primary end point was time to disease progression. A total of 116 patients were randomly assigned to the three treatment groups. At the time of a planned interim analysis, the median time to progression was significantly increased to 4.8 months in the patients receiving the 10 mg/kg dose of bevacizamab, compared with 2.5 months for placebo. Responses were noted only in the group treated with bevacizumab at 10 mg/kg, with four patients (10%) having partial tumor regressions.[12] The increase in time to progression was significant, accrual to the trial was stopped, and a lack of an effect on survival was attributed to the cross-over design.

Two large randomized trials currently underway are comparing progression-free and overall survival in untreated patients receiving the combination of bevacizumab plus IFNα or IFNα alone (with or without placebo). One is an industry-sponsored trial being conducted in Europe, and the second is an intergroup trial coordinated through the Cancer and Leukemia Group B (CALGB). These two randomized phase III trials have completed accrual and will assess the activity of bevacizumab plus IFNα in patients with mRCC. The studies are powered to demonstrate an increase of median survival. The activity of bevacizumab monotherapy will not be addressed directly, however, except for the suggestion of improved progression-free survival seen in first-line therapy in a randomized phase II trial.[22] Whether these studies will justify the use of bevacizumab alone in first-line therapy (because no monotherapy arm was included, this is not clear), or whether combination with interferon will be the preferred regimen, are important issues to be addressed.

Other Selected, Promising Agents

There are several VEGFR targeted tyrosine kinase inhibitors under study in RCC in addition to sorafenib and sunitinib. One is

pazopanib, which completed phase I evaluation and is currently being evaluated in a randomized discontinuation trial in the United States and a pivotal phase III trial in Europe. A second is AG013736, which showed a 40% response rate in a phase II trial conducted in 52 patients with cytokine-refractory mRCC.[39] A phase II trial is under way for AG013736 in patients who develop progressive disease after therapy with sorafenib. Given the activity of sunitinib and sorafenib, antitumor activity for these agents and other VEGFR and PDGFR targeted therapies is anticipated.

RAD001 (everolimus) is an orally administered mTOR inhibitor that showed antitumor activity in achieving objective response as well as prolonged time to progression in single-arm phase II trial in heavily pretreated patients.[40] A pivotal, randomized trial comparing RAD001 with placebo in patients who progressed to sunitinib or sorafenib therapy is planned.

VEGF-trap, a fusion protein composed of VEGFR fused to human immunoglobulin G (IgG), also binds serum VEGF.[41] A phase I trial of VEGF-trap in 15 patients with advanced solid malignancies did not produce objective responses, but one patient with RCC maintained stable disease for over 6 months.[41] Further assessment of activity for this agent in a phase II trial for patients with mRCC is underway.

COMBINATION STUDIES

One way to enhance the activity of the targeted approach to RCC therapy may be to combine agents that target different points in the VHL–hypoxia-inducible gene pathway[42] Examples would be the combination of a mTOR inhibitor such as temsirolimus (or RAD001) with sunitinib (or sorafenib), inhibitor of VEGFR; or bevacizumab with any of the aforementioned drugs (Fig 1). Phase I and II trials evaluating the safety and efficacy of these combinations is underway. This strategy utilizes agents that target the VHL–hypoxia-inducible gene pathway. Also, combining agents targeting the VHL–hypoxia inducible gene pathway with agents that target an entirely different pathway, which may be involved in angiogenesis or RCC growth, would be of high priority.

Combinations that show promise and favorable safety profiles in these trials will need to be assessed in randomized trials to define the benefit of utilizing the end points of progression-free survival and overall survival. Until definitive studies show conclusive evidence, combinations of targeted agents or targeted agents plus cytokines should not be administered outside of a clinical trial setting.

Following this concept, a first attempt at combination therapy was the combination of bevacizumab plus erlotinib. A phase II study evaluated advanced RCC patients treated with erlotinib and bevacizumab. Of 59 assessable patients, responses were achieved in 15 patients (25%).[43] Median progression-free survival was 11 months, with 60% of patients alive at 18 months.[43] The outcome of this trial led to a randomized phase II trial comparing bevacizumab plus erlotinib with bevacizumab plus placebo. The randomized phase II trial failed to show improvement in response rate or progression-free survival for the combination program.[22] The outcome of this randomized phase II trial highlights the importance of patient selection factors and of assessing new combination therapies in randomized trials. The patient population treated by Hainsworth et al[43] included mostly previously untreated patients, whereas the population reported in the earlier phase II had progressive RCC following treatment with high-dose IL-2.[12]

Combinations of targeted agents with cytokines are being studied. There have been several trials of sorafenib plus IFNα that established a safe dose and tolerability. One trial reported a high response rate,[44] but this was not confirmed in a second trial.[45] Combinations of targeted agents with cytotoxic agents are also underway, but will likely prove to be useful only in other malignancies, because cytotoxic agents have no activity in the treatment of clear-cell RCC.

NON–CLEAR-CELL TYPES

Several non–clear-cell histologies are associated with specific mutations. For example, type 1 papillary RCC is characterized by mutations in the tyrosine kinase domain of the *c-Met* oncogene.[46] Activating mutations in the tyrosine kinase domain of the *c-Met* gene on the *chromosome 7* gene were linked to development of hereditary papillary RCC as well as to a subset of patients with sporadic papillary RCC type I.[47] Studies are being directed to the manipulation of the c-Met protein in the papillary subset of RCC patients. The identification of targets and the study of relevant agents in non–clear-cell RCC is warranted, but is challenging because of the relative rarity of these tumor types.

PATIENT MANAGEMENT

For many years, there was a lack of new agents showing efficacy in patients with mRCC beyond IFNα and IL-2. As our review shows, several agents now show promising activity in this disease and are changing patient management. Both sunitinib and sorafenib were US Food and Drug Administration approved on the basis of studies performed in second-line therapy after progression to cytokine treatment, with benefit established through different trial designs and end points. Sorafenib was associated with a modest objective response rate, and clinical benefit is represented by prolongation of progression-free survival compared with placebo in a randomized phase III trial.[11,30] Sunitinib was approved based on two single-arm studies in second-line therapy that showed a high objective response rate compared with historical control.[32] Both of these agents represent viable treatment options in this setting.

Two randomized phase III trials established superiority of targeted therapy over standard cytokine therapy (IFNα) in first-line treatment. The eligibility criteria for the sunitinib phase III trial was broad, and the trial was directed to a relatively general population of patients with mRCC.[20] The primary objective of the trial (ie, benefit in progression-free survival over cytokine) was met in an interim analysis.[20] Eligibility for the temsirolimus phase III trial was restricted to patients with poor-risk features according to a modification of the MSKCC criteria.[21] Approximately 20% of this group comprises patients with mRCC,[48] and the benefit for temsirolimus is improved patient survival. The relative efficacy of temsirolimus as first-line therapy for patients with more favorable prognostic features warrants study.

One important aspect of patient management is whether there is benefit in sequencing these agents after progression to a prior targeted therapy agent. Recent data suggest that patients receiving previous

therapy with various targeted agents may derive some clinical benefit with a second targeted therapy.[49,50]

To date, no systemic therapy has proven useful in preventing relapse after nephrectomy for completely resected, localized RCC. One randomized phase III trial comparing sorafenib with placebo in the adjuvant setting recently began accrual in Europe. A second, National Cancer Institute (National Institutes of Health, Bethesda, MD) –sponsored phase III trial in the planning stage will compare sorafenib and sunitinib to placebo. Data from both trials will not be available for between 5 and 10 years. Unless the results of one or both of these trials show a benefit in relapse-free or overall survival, the standard of care remains observation alone after nephrectomy for localized RCC.

CONCLUSION

The small molecule targeted inhibitors sunitinib, temsirolimus, and sorafinib, and the monoclonal antibody bevacizumab, demonstrated antitumor activity in randomized trials. Superior activity was shown in randomized phase III trials for sunitinib and temsirolimus over cytokines in first-line therapy. Sorafenib and bevacizumab showed improved progression-free survival compared with placebo in randomized phase III and phase II trials, respectively. Sunitinib and sorafenib were recently approved by regulatory agencies in the United States and are being implemented in clinical practice. Further studies exploring combinations of these agents as well as other novel targeted drugs are warranted. Remaining questions need to be addressed by continued study. These include the role of combined targeted therapy, the optimal sequence as first-, second-, and third-line therapy, the timing of discontinuing targeted therapy in patients who show slow progression, the roles of cytoreductive nephrectomy and surgical resection of metastases in responding patients, the role of adjuvant therapy, and the prediction of outcome through clinical and tumor-specific prognostic criteria.

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Acknowledgment

We thank Carol Pearce, MFA, writer-editor in the MSKCC Department of Medicine Editorial Unit, for her critical review of this manuscript, and Tony J. Riley BFA, biomedical illustrator, medical graphics, MSKCC, for illustration.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Ronald M. Bukowski			Antigenics; Glaxo Smith Kline; Bayer; Novartis; Pfizer		Pfizer; Antigenics; Genentech; Onyx; Bayer	Amgen; Glaxo Smith Kline; Antigenics; Bayer; Pfizer; Genentech; Wyeth		

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